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(21) International Application Number: PCT/EP97/02577 (22) International Filing Date: 21 May 1997 (21.05.97) (30) Priority Data: MI96A001168 7 June 1996 (07.06.96) IT (71) Applicant (for all designated States except US): INDENA S.P.A. [IT/IT]; Viale Ortles, 12, I-20139 Milano (IT). (72) Inventor; and (75) Inventor/Applicant (for US only): BOMBARDELLI, Ezio [IT/IT]; Via Val di Sole, 22, I-20141 Milano (IT). (74) Agent: SPADARO, Marco; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: COLCHICINE-SKELETON COMPOUNDS, THEIR USE AS MEDICAMENTS AND COMPOSITIONS CONTAINING THEM (57) Abstract The present invention relates to colchicine and thiocolchicine derivatives which can be obtained from these molecules by functionalization of the C-7 to ketone or functionalization of the amino group. Said compounds have a marked antitlastic activity both on the normal cancer cells and on the chemoresistant phenotype. The compounds of the invention can be administered both by injection and orally.		

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COLCHICINE-SKELETON COMPOUNDS. THEIR USE AS MEDICAMENTS
AND COMPOSITIONS CONTAINING THEM

Technological background

The present invention relates to novel colchicine derivatives having antiproliferative, antineoplastic and antiinflammatory activities, the methods for the
5 preparation thereof and the pharmaceutical formulations containing them.

Colchicine is a known pseudo-alkaloid widely used for a very long time in therapy for the treatment of gout, a pathology on which it acts very quickly and
10 specifically, even though it should be used for short times due to its toxicity. A colchicine derivative, namely thiocolchicoside, is widely used to treat contractures and in inflammatory conditions on skeletal muscles. In addition, colchicine is a very potent
15 antitubercular agent, which acts blocking the formation of the mitotic spindle during cell division; this latter aspect has been investigated thoroughly for any antineoplastic activity and a great deal of colchicine derivatives have been prepared to this purpose.
20 Colchicine as such and a number of its derivatives could not be used clinically due to their high toxicity, and therefore their unacceptable risk/benefit ratio. Only one colchicine derivative, demecolcine, is used in some degree in oncology for the treatment of some leukemia
25 forms.

Therefore the problem exists of the availability of antineoplastic medicaments having a satisfactory risk/benefit ratio, i. e. a high therapeutical activity

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with poor or no side-effects.

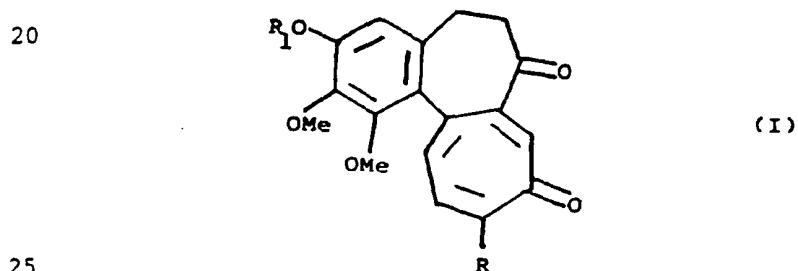
Another problem in the antineoplastic field is the resistance to the medicament which takes place in specific phenotypes.

5 Now it has surprisingly been found that some colchicine derivatives have a high cytotoxic activity both on the normal cancerous cells and on the corresponding resistant phenotype (MDR).

10 The compounds of the invention are potent apoptosis inducers, proving to be markedly better than the compounds of the prior art. Due to their lipophilic, characteristics, the compounds are particularly bioavailable after oral administration. Moreover, the compounds of the present invention can be administered
15 by the parenteral or topical routes as well.

Disclosure of the invention

The present invention relates to compounds of formula (I)



wherein R is a methoxy or methylthio group and R₁ is a straight or branched alkyl or alkenyl group having 1 to 6 carbon atoms, or an alicyclic or heterocyclic moiety,
30 a saturated or unsaturated mono or dicarboxylic or amino acidic acyl residue or a β-D-glucose or 6-deoxygalactose

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residue.

Examples of alkyl group are methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, t-butyl, pentyl, neopentyl, hexyl.

5 Examples of alkenyl group are propenyl, 1-butenyl, 2-butenyl, 1-pentenyl.

Examples of alicyclic group are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

10 Examples of heterocyclic group are benzotriazolyl, methyltetrazolyl.

Examples of acyl residue are ximenoyl, succinyl, aspartyl.

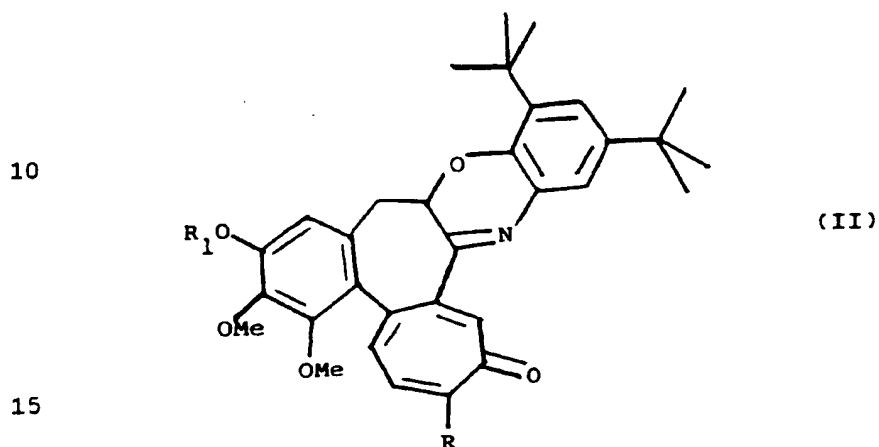
The compounds of formula I are prepared starting from the natural compounds colchicine or thiocolchicine or from the C3-derivatives thereof commercially available or obtainable with methods known in literature. As described in literature, the C3 derivatives can be prepared reacting the 3-O-dimethyl derivative with an alkyl or acyl halide. The hydrolysis of said compounds with strong mineral acid aqueous solutions allows to obtain selectively, changing the temperature and the reaction time, the corresponding N-deacetyl derivatives. In particular, the deacetylation of thiocolchicine or of the C3 derivatives thereof can be carried out subjecting the compounds to acidic hydrolysis; in the case of thiocolchicine, the hydrolysis with halo acids or, more preferably, with sulfuric acid (20% H_2SO_4 - 120 h), allows to obtain N-deacetylthiocolchicine and 3-demethyl-N-deacetylthiocolchicine in nearly quantitative yields.

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The N-d acetyl derivatives are reacted with 4-

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formyl-1-methylpyridinium-p-toluenesulfonate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to prepare the compounds of formula I.

Alternatively, reacting the N-deacetyl derivatives
5 with 2,3-ditert-butyl-1,2-benzoquinone, the compounds of formula II are obtained:



wherein R and R₁ have the meanings described above.

A further of the present invention are the compounds of formula II.

20 The compounds object of the invention exhibit a remarkable antineoplastic activity both *in vitro* and *in vivo*.

The table shows the antimitotic activity of the compounds of the invention on cultured breast tumour
25 explants normal (MCF-7) or resistant to both adriamycin and vinblastin (MCF7-ADR), compared with colchicine and taxol.

5
TABLE

Compounds	IC ₅₀ (nM)		
	MCF7-ADR	MCF-7	MCF7-ADR/MCF7
Colchicine	12,000	1.8	6,600
Compound Ia	15	6.2	2.4
Compound Ib	40	23	1.7
Compound IIa	52	17	3.0
Taxol	2,400	2.3	1,043

15 This table evidences that the compounds of the invention have significant advantages on the resistant cell lines, which are nowadays considered the main target of cytotoxic medicaments.

20 Moreover, the compounds according to the present invention have antiinflammatory and antiarthritis activities (degenerative rheumatoid arthritis and similar pathologies) and they can be incorporated in pharmaceutical formulations useful for the administration of the medicament for the indicated pathology. Formulations for the intravenous, oral, 25 transdermal, epicutaneous administrations can conveniently be prepared.

Among the excipients useful to prepare said formulations, natural and synthetic phospholipids proved to be particularly useful for preparing liposomal forms 30 for the parenteral and/or topical routes. The same formulations proved to be useful in the topical

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treatment of cutaneous epitheliomas and in cutaneous hyperproliferative conditions, such as psoriasis. In the specific antineoplastic field, besides the phospholipids which allow the administration of the medicament in the liposomal form, some surfactants such as polyethoxylated castor oils or polysorbates acting synergistically with the active ingredient, turned out to be particularly useful. Preferably the active principle is micronized to dissolve the compound in water. A surprisingly active, convenient form is the complex of these compounds with cyclodextrins.

In oncology, the products are used at dosages from 1 to 100 mg/m².

The following examples further illustrate the invention.

Example 1

Preparation of Thiocolchicone from N-deacetylthiocolchicine

(Ia: R = SMe; R₁ = Me)

100 ml of CH₂Cl₂ and 30 ml of DMF are mixed under nitrogen atmosphere, then 4 g of deacetylthiocolchicine (M.W. 373, 10.7 mmol) and 24,2 g of 4-formyl-1-methylpyridinium p-toluenesulfonate (M.W. 279, 15 mmol) are added; the whole is refluxed for 3 hours or anyhow until the amine disappears. The solution is cooled at 0°C and then added with 1.94 g of DBU (M.W. 152, 12,8 mmol), drop by drop, to obtain a dark red solution. After 15 minutes, 150 ml of an oxalic acid aqueous solution are added, the mixture is left to react overnight, then repeatedly extracted with CH₂Cl₂; dried over sodium sulfate and the solvent is evaporated off to

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dryness. The residue is crystallized from ethyl acetate to obtain a 78% yield. Thiocolchicone has the following chemical-physical and spectroscopical characteristics.

M.p. 212°C

5 MS (E.I.): 372 m/z (35%) - 344 (55%) - 329 (6%) - 311 (13%) - 301 (4%) - 287 (8%) - 267 (4%) - 243 (4%) - 215 (4%) - 84 (64%) - 49 (100%).

¹H-NMR (300 MHz, CDCl₃)

	ppm	molt	int	type	J(Hz)	J(Hz)	J(Hz)
10	2.45	s	3H	SME			
	2.68	ddd	1H	H-5eq.	13.4	4.8	1.9
	2.81	ddd	1H	H-6ax	16.6	13.4	4.8
	2.95	ddd	1H	H-6eq	16.6	5.5	1.9
	3.11	ddd=td	1H	H-5ax	13.1	13.5	5.6
15	3.57	s	3H	OMe			
	3.88	s	3H	OMe			
	3.90	s	3H	OMe			
	6.56	s	1H	H-4			
	6.96	s	1H	H-8			
20	7.07	AB	1H	H-11	10.2		
	7.27	AB	1H	H-12	10.2		

¹³C-NMR (300 MHz, CDCl₃):

15.8 ppm (SMe) - 30.0 (C-5) - 48.0 (C-6) - 56.7 (OMe-3) - 61.8 (OMe-2) - 61.8 (OMe-1) - 107.8 (C-4) - 125.3 (C-12b) - 127.0 (C-11) - 130.7 (C-8) - 134.4 (C-4a) - 136.1 (C-12a) - 136.5 (C-12) - 142.3 (C-2) - 150.4 (C-1) - 152.6 (C-7a) - 154.6 (C-3) - 160.7 (C-10) - 182.9 (C-9) - 206.2 (C-7).

Example 2

30 Preparation of colchicone from N-deacetyl-colchicine
(Ib : R = OMe; R₁ = Me)

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3.58 g of N-deacetylcolchicine are treated according to the procedure of Example 1. 2.6 g of colchicone are obtained, having the following chemical-physical and spectroscopical characteristics.

5 MS (E.I.): 356 m/z (100%) - 328 (95%) - 313 (25%) - 300 (22%) - 285 (18%) - 271 (26%) - 253 (13%) - 238 (8%) - 227 (13%) - 199 (16%) - 171 (11%).

¹H-NMR (300 MHz, CDCl₃)

	ppm	molt	int	type	J(Hz)	J(Hz)	J(Hz)
10	2.67	ddd	1H	H-5β	13.7	5.0	2.2
	2.82	ddd	1H	H-6β	16.6	13.6	5.0
	2.95	ddd	1H	H-6α	16.6	5.4	2.2
	3.11	ddd	1H	H-5α	13.7	13.6	5.4
	3.55	s	3H	OMe-1			
15	3.86	s	3H	OMe-2			
	3.87	s	3H	OMe-3			
	4.00	s	3H	OMe-10			
	6.54	s	1H	H-4			
	6.85	d	1H	H-11	10.7		
20	7.12	s	1H	H-8			
	7.24	d	1H	H-12	10.7		

¹³C-NMR (300 MHz, CDCl₃):

29.27 ppm (C-5) - 43.33 (C-6) - 55.96 (OMe-10) - 56.44 (OMe-3) - 61.07 (OMe-2) - 61.12 (OMe-1) - 106.96 (C-4) -
 25 112.40 (C-11) - 124.50 (C-12b) - 132.00 (C-4a) - 132.80 (C-8) - 135.30 (C-12) - 136.15 (C-12a) - 141.80 (C-2) - 150.16 (C-1) - 151.83 (C-7a) - 153.70 (C-3) - 164.10 (C-10) - 179.40 (C-9) - 205.60 (C-7).

Example 3

30 Preparation of the condensation product between Thiocolchicine and 3,5-ditert-butyl-1,2-benzoquinone

(IIa: R = SMe; R₁ = Me)

500 mg of deacetylthiocolchicine (M.W. 373, 1.34 mmol) and 590 mg of 3,5-di-tert-butyl-1,2-benzoquinone (M.W. 220, 2.69 mmol) are dissolved in 50 ml of methanol, under normal atmosphere.

The reaction is followed by TLC (CH₂Cl₂:acetone 30:1) and after about 18 hours the solvent is evaporated off under vacuum.

The warm crude is dissolved in 1 volume of ethyl acetate, 1-1.5 volumes of hexane are added and the mixture is cooled on ice. The reaction product is recovered by filtration, the yield being 70%. This compound has the following chemical-physical and spectroscopical characteristics.

M.p. 238°C with decomposition

MS (E.I.): 573 m/z (33%) - 558 (1%) - 545 (100%) - 530 (9%) - 514 (7%) - 314 (4%) - 301 (4%) - 265 (7%) - 249 (7%).

¹H-NMR (300 MHz, CDCl₃)

	ppm	molt	int	type	J(Hz)	J(Hz)
20	1.30	s	9H	tBu		
	1.40	s	9H	tBu		
	2.45	s	3H	SMe		
	3.05	dd	1H	H-5	14.0	4.0
25	3.30	dd	1H	H-5	14.0	4.0
	3.55	s	3H	OMe		
	3.83	s	3H	OMe		
	3.87	s	3H	OMe		
	3.86	t	1H	H-6	4.0	
30	6.65	s	1H	H-4		
	7.08	d	1H	H-11	11.0	

			10		
	7.20	d	1H	H-5'	2.0
	7.26	d	1H	H-3'	2.0
	7.28	d	1H	H-12	11.0
	7.33	s	1H	H-8	
5	¹³ C-NMR (300 MHz, CDCl ₃):				
	15.71 ppm (SMe) - 30.33 (C(CH ₃) ₃) - 31.95 (C(CH ₃) ₃) -				
	34.96 ((C(CH ₃) ₃) - 35.25 (C(CH ₃) ₃) - 36.60 (C-5) - 56.41				
	(OMe-3) - 61.81 (OMe-1) - 61.64 (OMe-2) - 76.47 (C-6) -				
	109.80 (C-4) - 123.56 (C-5') - 124.61 (C-3') - 125.75				
10	(C-12b) - 126.80 (C-11) - 132.28 (C-4') - 133.58 (C-6')				
	- 135.13 (C-8) - 135.47 (C-4a) - 136.10 (C-12) - 137.01				
	- (C-12a) - 142.35 (C-2) - 143.21 (C-7a) - 144.88 (C-				
	2') - 147.19 (C-1') - 152.06 (C-1) - 153.78 (C-3) -				
	159.85 (C-10) - 164.68 (C-7) - 182.26 (C-9).				

15 Example 4

Preparation of tablets containing compound (Ia)

	Compound Ia	25 mg
	Lactose	47 mg
	Microcrystalline cellulose	20 mg
20	Cross-linked sodium carboxymethyl cellulose	5 mg
	Colloidal silica	1 mg
	Talc	1 mg
	Magnesium stearate	1 mg

Example 5

25 Preparation of a liposome cream containing compound (IIa)

	Compound IIa	0.20 g
	Phosphatidylcholine	20.00 g
	Cholesterol	0.50 g
30	Butylhydroxytoluene	0.01 g
	95% Ethanol	8.00 g

	11	
	Disodium edetate	0.15 g
	Imidazolidinyl urea	0.30 g
	Sodium dehydroacetate	0.20 g
	Hydroxyethyl cellulose	
5	(Natrosol 250 HHX-Aqualon)	2.00 g
	Distilled water	67.75

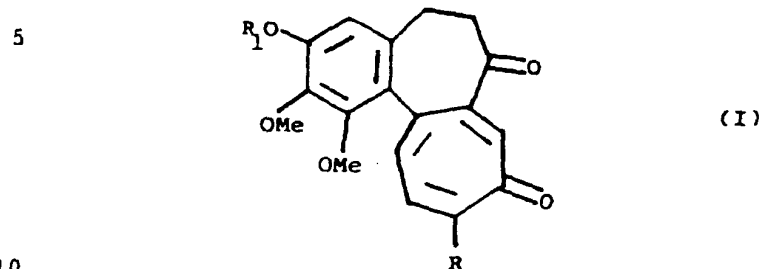
Example 6

	Preparation of an injectable solution containing	
	compound (Ia)	
10	Compound Ia	15 mg
	PEG-660 12-hydroxystearate	2.500 mg
	Propylene glycol	1.000 mg
	alcohol q.s. to	5 ml

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CLAIMS

1. Compounds of formula I



wherein R is a methoxy or methylthio group and R₁ is a straight or branched alkyl or alkenyl group having 1 to 6 carbon atoms, or an alicyclic or heterocyclic moiety, a saturated or unsaturated mono or dicarboxylic or amino acidic acyl residue or a β-D-glucose or 6-deoxygalactose residue.

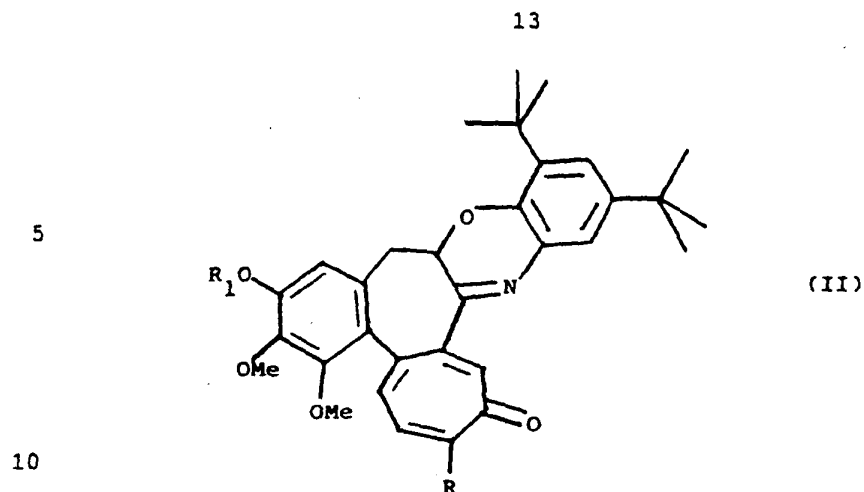
2. Compounds according to claim 1, wherein R is methoxy.

- 20 3. Compounds according to claim 1, wherein R is methylthio.

4. Compound according to claim 2, wherein R₁ is methyl.

5. Compound according to claim 3, wherein R₁ is methyl.

- 25 6. Compounds of formula II



wherein R and R₁ have the meanings defined in claim 1.

7. Compounds according to claim 6, wherein R is methoxy.

15 8. Compounds according to claim 6, wherein R is methylthio.

9. Compound according to claim 8, wherein R₁ is methyl.

10. A process for the preparation of the compounds of claims 1-5, which comprises reacting N-deacetylcolchicine or N-deacetylthiocolchicine with 4-formyl-1-methylpyridinium p-toluenesulfonate and 1,8-diazabicyclo[5.4.0]undec-7-ene.

25 11. A process for the preparation of the compounds of claims 6-9, which comprises reacting N-deacetylcolchicine or N-deacetylthiocolchicine with 3,5-ditert-butyl-1,2-benzoquinone.

12. The use of the compounds of the claims 1-9 as medicaments.

30 13. The use of the compounds of claims 1-9 for the preparation of a medicament with antineoplastic or

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antiproliferative activity.

14. The use of the compounds of claims 1-9 for the preparation of a medicament with antiinflammatory and antiarthritis activities.

5 15. Pharmaceutical compositions containing an effective amount of a compound of claims 1-9.

16. Compositions according to claim 15, suitable for the parenteral administration.

10 17. Compositions according to claim 15, suitable for the enteral administration.

18. Compositions according to claim 15, suitable for the topical administration.

19. Compositions according to claim 16 or 18 in the form of liposomal formulations.

15 20. Compositions according to any one of claims 15-19, containing a surfactant, such as polyethoxylated castor oil or a polysorbate.

20 21. Compositions according to any one of claims 15-19, containing the active ingredient in the form of a complex with cyclodextrin.

INTERNATIONAL SEARCH REPORT

Intern. Appl. No.
PCT/EP 97/02577

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C49/755 C07C323/22 C07D265/34 C07H15/248 A61K31/12
A61K31/10 A61K31/70 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 3 032 M (ROUSSEL-UCLAF) 28 December 1964 see the whole document ---	1,2,4, 12-18
X	AUST. J. CHEM. (AJCHAS,00049425);92; VOL.45 (10); PP.1577-88, UNIV. MELBOURNE;SCH. CHEM.; PARKVILLE; 3052; AUSTRALIA (AU), XP002038712 BANWELL M G ET AL: "Semisyntheses, x-ray crystal structures, and tubulin-binding properties of 7-oxodeacetamidocolchicine and 7-oxodeacetamidoisocolchicine" see pages 1579 and 1585 see compound 2 --- -/--	1,2,4, 10,12,13

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

25 August 1997

Date of mailing of the international search report

03.09.97

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Interns J Application No

PCT/EP 97/02577

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. NAT. PROD. (JNPRDF,01633864);90; VOL.53 (3); PP.623-9, PENNSYLVANIA STATE UNIV.;DEP. CHEM.; UNIVERSITY PARK; 16802; PA; USA (US), XP002038713 AL-TEL T H ET AL: "New natural colchicinoids: indications of two possible catabolic routes for the colchicine alkaloids" see compound 9 see page 626 ---	1,2
P,X	J. MED. CHEM. (JMCMAR,00222623);97; VOL.40 (6); PP.961-966, UNIVERSITY OF NORTH CAROLINA;NATURAL PRODUCTS LABORATORY DIVISION OF MEDICINAL CHEMISTRY AND NATURAL PRODUCTS SCHOOL OF PHARMACY; CHAPEL HILL; 27599; NC; USA (US), XP002038714 SHI Q ET AL: "Antitumor Agents. 172. Synthesis and Biological Evaluation of Novel Deacetamidothiocolchicin-7-ols and Ester Analogs as Antitubulin Agents" see compound 8 see page 962 ---	1,3,5, 10,12,13
A	FR 2 019 M (CIBA SOCIÉTÉ ANONYME) 16 September 1963 see claims ---	1,12,13
A	US 4 349 548 A (JONES JAMES H) 14 September 1982 see claims -----	1,12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No.
PCT/EP 97/02577

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 3032 M		US 3442953 A	06-05-69
FR 2019 M		NONE	
US 4349548 A	14-09-82	EP 0080116 A	01-06-83
		JP 58092671 A	02-06-83

Form PCT/ISA/210 (patent family annex) (July 1992)